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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/699,580	10/30/2000	David H. Beach	GPCI-P10-019	8428

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EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 10/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/699,580	BEACH ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *March 29, 2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of group II, claims 37-44 in the reply filed on July 12, 2004 is acknowledged. Applicant's traversal arguments are moot since the claims to the non-elected invention have been canceled.

The requirement is still deemed proper and is therefore made FINAL.

Specification

The abstract of the disclosure is objected to because of undue length, it should contain no more than 150 words. Correction is required. See MPEP § 608.01(b).

Additionally, the examiner requests the abstract be edited to remove embodiments not claimed in the instant application and to more fully describe the embodiments of the invention now being described, i.e. methods of inhibiting transcription and/or translation of mammalian CDC25A genes.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 37-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 37 recites a method of inhibiting expression of

mammalian CDC25A gene by contacting the gene with an oligonucleotide that "hybridizes...under stringent conditions of 5-10^{O}C below the calculated melting temperature...of said sequence." It is unknown what is meant by this limitation.

1. If a specific sequence is not recited, how can the melting temperature be calculated? Is it meant that the melting temperature should be calculated for any probe/target combination and then the contacting step should be carried out at a temperature that is 5-10^{O}C below this temperature, for example? It appears that almost any sequence might be used with the claimed method simply by choosing an appropriate temperature at which the contacting step is to be done. What exactly are the stringent conditions? Is the temperature at which hybridization is done the only condition? Hybridization conditions are not explicitly defined in the specification. The only mention of hybridization conditions with respect to nucleotides in the specification is on page 24, lines 13-17, which simply states that hybridization conditions can be varied and either low or high stringency conditions can be used.

2. Reference is made to the laboratory manual of Sambrook et al. but no specific chapters or sections numbers are used. This manual has many different hybridization conditions in it. How is one of skill in the art to know which of the many ones recited in Sambrook et al. is meant in the claim as written?

3. Claims 38-44 are rejected for the same reasons as they are dependent on claim 37.

4. Because the meaning of this limitation cannot be determined, for the purposes of examination, the recitation of hybridization conditions has not been given patentable weight.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 37-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

5. Claims 37-44 are drawn to a method of inhibiting expression of the gene that encodes mammalian CDC25A protein by contacting the gene with an oligonucleotide capable of hybridizing to the gene. As described in the previous enablement rejection, the claims encompass inhibition of this gene in any mammalian animal, including humans. The claimed method encompasses inhibition of gene expression in many different mammals and each mammal may be treated by many different oligonucleotides capable of hybridizing to the target gene.

The specification provides no written description to support the broad genus of oligonucleotides and mammals encompassed by the claims. The specification teaches

on page 26, lines 3-10: "In one embodiment, complex formation is prevented in an indirect manner, such as by preventing transcription and/or translation of the cdc25 DNA and/or RNA. This can be carried out by introducing into cells antisense oligonucleotides which hybridize to the cdc25-encoding nucleic acid sequences, and thus prevent their further processing." This constitutes the sole disclosure with regard to the claimed invention. There is no description of what portion of CDC25A should be targeted, or even which CDC25A should be targeted. Claim 37 is drawn to a method of inhibiting transcription or translation of a polynucleotide encoding mammalian CDC25A protein, only the human CDC25A protein and the gene encoding it (SEQ ID NOS: 2 and 1, respectively) has been described in the specification. However, claim 37 is directed to encompass gene sequences, sequences that hybridize to SEQ ID NO: 1, corresponding sequences from other species, mutated sequences, allelic variants, splice variants and so forth. None of these sequences meet the written description provision of 35 USC 112, first paragraph. The specification provides insufficient written description to support the genus encompassed by the claim. Not only is the target not fully described; there is no description as to how to perform the claimed method. No specific structures capable of inhibiting expression of any CDC25A or CDC25A variant encompassed by claim 37 are disclosed. There are no examples of antisense oligonucleotides being used *in vitro* or *in vivo* to inhibit transcription or translation of any CDC25A.

6. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought,

he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

7. MPEP 2163 states in part, "An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004) (The patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product, however the patent did not disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "[w]ithout such disclosure, the claimed methods cannot be said to have been described.")."

8. The skilled artisan cannot envision the detailed structure of the encompassed antisense sequences, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai

Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

9. Therefore the full breadth of the claims does not meet the written description provision of 35 USC 112, first paragraph. No specifically disclosed structures of sequences of oligonucleotides capable of inhibiting CDC25A expression are provided and the full breadth of the claimed genus is not described. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

10. Identification of oligonucleotides effective at inhibiting expression of one gene do not serve to identify effective inhibitors of any other gene. Identification of antisense and siRNA oligonucleotides that function to inhibit expression of a gene is an empirical process that must be repeated for each gene targeted.

Claims 37-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of inhibiting the transcription or translation of mammalian CDC25A protein *in vitro*, does not reasonably provide enablement for performing the claimed method *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

11. The following factors as enumerated *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), are considered when making a determination that a disclosure is not enabling: the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples and the quantity of experimentation needed to make the invention based on the content of the disclosure.

12. Claims 37-44 are drawn to a method of inhibiting the transcription and/or translation of a polynucleotide encoding mammalian CDC25A protein. The claims do not limit the method to exclude embodiments wherein the method is performed *in vivo* and in fact claim 44 specifically recites that the method is performed in a cell. The specification does not provided adequate disclosure to allow one of skill in the art to practice the claimed methods *in vivo*.

13. The specification teaches on page 26, lines 3-10: "In one embodiment, complex formation is prevented in an indirect manner, such as by preventing transcription and/or translation of the cdc25 DNA and/or RNA. This can be carried out by introducing into cells antisense oligonucleotides which hybridize to the cdc25-encoding nucleic acid sequences, and thus prevent their further processing." This constitutes the sole disclosure with regard to the claimed invention. There is no description of what portion of CDC25A should be targeted, or any guidance as to how to perform the claimed method. There are no examples of antisense oligonucleotides being used *in vitro* or *in vivo* to inhibit transcription or translation of CDC25A.

14. The state of the art prior art is such that inhibition of gene expression *in vitro* was known at the time of invention but inhibition of gene expression *in vivo* both at the time of invention and even to the present time was not routine for several reasons, including the problems of delivery, specificity and duration.

15. The problems of nucleic acid based therapies and antisense technology are well known in the art, particularly with regard to the inability to specifically deliver an effective concentration of a nucleic acid to a target cell, such that a target gene is inhibited to a degree necessary to result in a therapeutic effect. For example, at the time the instant invention was made, the therapeutic use of nucleic acids was a highly unpredictable art due to obstacles that continue to hinder the therapeutic application of nucleic acids *in vivo* (whole organism) (see for example Agrawal et al. (Molecular Medicine Today, 2000, vol 6, p 72-81), Branch (TIBS 1998, vol. 23, p. 45-50) and Jen et al. (Stem Cells 2000, Vol. 18, p 307-319)). Such obstacles include, for example, problems with delivery, target accessibility and the potential for unpredictable nonspecific effects.

16. Jen et al. state (see page 313, second column, second paragraph) "One of the major limitations for the therapeutic use of AS-ODNS and ribozymes is the problem of delivery.... presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

17. Opalinska et al. (Nature Review, 2002, vol 1, p. 503-514) state "[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA" and in column 2 of the same page, "Another problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded."

18. Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo* in all mammals, with a resultant inhibition of gene expression, as claimed. The specification provides no examples of *in vivo* inhibition of gene expression. The skilled artisan would not know *a priori* whether introduction of antisense oligonucleotides *in vivo* by the broadly disclosed methodologies of the instant invention, would result in successful inhibition of expression of the target gene. One of skill in the art would not know how to deliver oligonucleotides to a mammal in such a way that would ensure an amount sufficient to modify or inhibit expression of a target gene is delivered to the proper cell.

19. In fact, the state of the art is such that successful delivery of oligonucleotide sequences *in vivo* or *in vitro*, such that the polynucleotide or oligonucleotide provides the requisite biological effect to the target cells/tissues/organs, must be determined empirically. Methods of inhibiting gene expression using nucleic acids *in vivo* are unpredictable with respect to delivery of the nucleic acid molecule such that the nucleic acid molecule is targeted to the appropriate cell/organ, at a bioeffective concentration and for a period of time such that the nucleic acid molecule is effective in, as in the instant application, attenuating or inhibiting expression of a target gene such that the organism exhibits a loss of function phenotype.

20. The specification does not provide the guidance required to overcome the art-recognized unpredictability of using antisense oligonucleotides in therapeutic applications in any mammal. The field of antisense therapeutics does not provide that guidance, such that the skilled artisan would be able to practice the claimed therapeutic methods.

21. Thus, while the specification is enabling for inhibition of CDC25A gene expression *in vitro*, the specification is not enabling for the broad claims of inhibiting the expression of CDC25A in a mammal, as the art of inhibiting gene expression by introducing antisense oligonucleotides into an organism is neither routine nor predictable. In order to practice the claimed invention *in vivo* in all mammals a number of variables would have to be optimized, including 1). determining what sequences would constitute antisense sequences capable of binding to CDC25A and what antisense sequences would actually bind to CDC25A and form a strong enough

complex that they would be effective at inhibiting transcription or translation, 2). the form of the antisense oligonucleotide, whether to use a modified oligonucleotide with one or more backbone, sugar or base modifications, 3). the mode of delivery of the antisense oligonucleotide to an organism that would allow it to reach the targeted cell, 4). the amount of antisense oligonucleotide that would need to be delivered in order to bind a sufficient amount of CDC25A to inhibit transcription or translation once it reached the proper cell and 5). ensuring the antisense oligonucleotide remains viable in a cell for a period of time that allows inhibition of transcription or translation to an extent that there is a measurable and significant therapeutic effect. Each one of these variables would have to be empirically determined for each antisense oligonucleotide. While optimization of any single one of these steps may be routine, when taken together the amount of experimentation required becomes such that one of skill in the art could not practice the invention commensurate in scope with the claims without undue, trial and error experimentation and therefore, claims 37-44 are not enabled.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Tracy Vivlemore
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Art Unit 1635

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